Is partnering an opportunity for a biotechnology company to grow or does it create risk?

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Abstract The prevailing business development model in the biotechnology sector is partnership with one or more large companies. There are now too many biotechnology companies and too few pharmaceutical companies for this to continue to be a viable strategy across the industry. The asymmetry of the relationship extends to risk; contrary to standard opinion the biotechnology company entering into a traditional partnering relationship enlarges its risk rather than reducing it. Alternative strategies are required.

Introduction

The biotechnology industry is very dependent on partnerships with larger companies. There is a prevalent view that partnerships between young and/or small biotechnology companies and large pharmaceutical, agrochemical or seed companies are essential for growth. This view is conditioned by the realisation that few, if any, biotechnology companies can realistically contemplate the previously favoured FIPCO (Fully Integrated Pharmaceutical COmpany) route. For example, Neose Technologies Inc., which specialises in oligosaccharides for therapeutic applications, stated in a funding prospectus:[1]

> 'The Company generally intends to develop its pharmaceutical products through pre-clinical development and initial clinical trial phases and to use strategic alliances with pharmaceutical companies to conduct late-stage clinical trials, to obtain regulatory approvals, and to market and sell the Company's products, in exchange for licence fees, milestone payments, and royalties.'

However, several events, some recent and some much longer ago, indicate that the partnership model, at least as currently practised, can lead to unacceptably high risks for a biotechnology company. The purpose of this paper is to explore the benefits and risks of partnerships and to

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indicate ways forward which may lead to a more acceptable balance.

Driving forces

Biotechnology has been characterised by scientific and technological innovation but also by extraordinary innovation in business structures and in financing strategies. This degree of innovation has been driven by the unique characteristics of the end-use industries, healthcare and agriculture primarily, that biotechnology aspires to serve. The rate of new product introductions in the pharmaceutical and agrochemical industries is affected by the intense regulatory oversight that they are subjected to in all developed countries to ensure safety and efficacy. The degree of this regulatory oversight is seldom appreciated beyond the immediate confines of these industries. A test-tube discovery of a new chemical entity (NCE), even one that is similar to an existing product (eg a penicillin antibiotic or a triazole fungicide), is the starting point of an eight to ten year path to first sales at a cost in the range of US$100m (for a 'me-too' agrochemical) up to US$500m (for a completely new therapeutic). It is a reasonable guess that these figures may well be rather conservative in the case of a new medicine which seeks to replace a damaged gene in humans suffering from, or likely to suffer from, diseases such as cystic fibrosis or breast cancer.

Software or Internet companies face neither the delay nor the regulatory cost burden familiar to biotechnology companies; if they are going to succeed or fail they will probably do so in a year or two and possibly at lower cost. Aeroplane manufacture is the only other industry that appears to have the same sort of long-term financial risk, grounded in regulatory controls, as pharmaceuticals and this is not an industry that small companies enter hopefully, or at all.

Thus, an inventor in the biological sciences, possibly in a university or a research organisation such as the National Institutes of Health (NIH) in the USA or the Medical Research Council (MRC) in the UK, faces a huge task and a large investment has to be made before the product concept can be marketed. The first stage is usually the creation of a specialist company with seed or venture finance; but this is still only the first stage. Much needs to be done to move the concept forward. It is for these reasons that the inventor and/or the new company that he/she forms is driven into innovative business and financing structures.

FIPCO – the previous model

When biotechnology companies were first set up in the mid-1970s, with Amgen, Genentech and Chiron among them, there was a view that they could establish themselves, over time, as true rivals to the existing pharmaceutical companies. Given success in R&D it was widely felt that they would be able to establish marketing, sales and distribution operations and also to manufacture their products. However, it was recognised that they might have to form some alliances in at least some countries; Amgen's early relationship with Kirin in Japan was an example. This was thought to be quite normal because many of the majors had deals of this type to access overseas markets while retaining control of their home territories. Even a large pharmaceutical company such as Glaxo worked in partnership with another major when it launched ranitidine (Zantac) in the USA.

Amgen retained a strong position in the sales and distribution of its products and could be said to have completed the path from research company to pharmaceutical company. It stands alone as a biotechnology company that became a FIPCO and had a market capitalisation of US$15bn by 1996.[2] Even Genentech and Chiron, the next two most successful biotechnology companies, were unable to achieve FIPCO status. While retaining operational independence they have had to sell very substantial proportions of their equity to major international pharmaceutical companies, Roche and Ciba (now Novartis),

respectively. Indeed, it was the purchase by Roche of a majority stake in Genentech that signalled unequivocally how extraordinarily difficult the FIPCO model is. This single event caused a major strategic shift throughout the biotechnology sector.

The partnership model

Currently, the most common biotechnology model involves establishing one or more relationships with large companies operating globally, or at least in most of the developed world. The basic concept was encapsulated in the earlier quotation from Neose. Most biotechnology companies now operate to this model, or aspire to do so.

The core problem for any biotechnology company is funding its existence through to the time at which profits can be generated. As noted, the FIPCO model demands that a company should have available as much as US$500m just to be permitted to enter the market with its first product. But this is only a beginning. A FIPCO would also need:

- Investment in sales and distribution infrastructure. The sales force needed to detail a therapeutic to general practitioners across the USA would be numbered in thousands. In-house international operations would call for as many again, even if focused only on the developed world. Marketing support would consume additional funds.
- Manufacturing plant to good manufacturing practice (GMP) standard.
- On-going R&D to support the product with line extension and to work on further products to follow.

Biotechnology companies have to find ways to ensure that all of this is available at an acceptable cost. Generally, they have sought to 'off-set' some, or even a large part, of the cost to others through partnerships. A working definition of a partnership in the sense usually used in the biotechnology sector is: 'a contractual arrangement whereby a smaller company obtains financial and other help from a larger company in exchange for giving up certain rights to its technology and/or products'.

Typically, biotechnology companies appear to have regarded a partnership with a big pharmaceutical company primarily as a route to funds; this might be achieved directly (from the partner) and also indirectly (from public markets) using the validation implied by the big company's interest. Further potential gains to the biotechnology company include access, formal or informal, to the clinical, manufacturing and marketing skills which the small company might find hard to duplicate on the back of a narrow product portfolio. Details of the motivations behind alliances were assessed[3] in 1994; access to capital was the most important factor, but not the only one.

Current partnership examples

In the 11 year period 1986–1996 it has been estimated that more than 1,630 alliances were formed by biotechnology companies[4] and that there has been a rising trend from 1986 when there were 40 examples to 236 such deals in 1996.

The content of these deals runs through the complete spectrum from simple licences for marketing rights to substantial equity investments. Typically, there may be an equity investment, an up-front fee and a commitment to royalties on sales under a licence which may be global or regional. The licence may also allow the licensor to retain some market entry rights in some territories through co-marketing (different brands) or co-promotion (perhaps to different sectors such as hospitals and general practice). The licensor may retain manufacturing rights or grant them. Usually there will be some obligation for the licensee to provide assistance and guidance in matters such as clinical development and regulatory approval; this is commonly the case where the licensor is relatively small and has not achieved the critical mass to be able to sustain the specialist staff for these activities.

Given the gamut of possible combinations that the parties may enter into, there is no

standard partnership deal. Hence, it would be improper to suggest that any of the following types of deals should be seen as standard; rather they should be seen as examples of what partnering arrangements might look like.

- Cantab Pharmaceuticals has no interest in becoming an animal health specialist but its DISC Virus technology is believed to have potential in that field to create vaccines against several important animal diseases. Cantab's solution was to grant Pfizer an extensive licence to DISC for animal applications in exchange for investment (Pfizer now owns about 5 per cent of Cantab), a fee and future royalties. Pfizer will undertake the development work.
- In 1996 Glaxo/Wellcome extended its R&D joint venture with Sequana to search for non-insulin dependent diabetes genes in extremely obese patients. Glaxo/Wellcome will have commercialisation rights to therapeutic products from the research while Sequana will have rights to any diagnostic products.
- NeuroSearch, based in Denmark, is due to receive some ECU23m in up-front and milestone payments from Bristol-Myers Squibb during the course of development of its Parkinson's disease drugs plus royalties (note that the size of some deals is inflated by including undiscounted estimates of royalties as well).

The risks of current partnership strategies

The biotechnology/pharmaceutical partnership is asymmetrical in two dimensions; it is these asymmetries that create risk for biotechnology companies entering partnerships with pharmaceutical companies.

There are many more biotechnology companies, probably in the order of 2,500 world-wide (Ernst & Young reports some 1,250 in the USA[2] and just over 700 in Europe[5]). There are fewer than 50 pharmaceutical companies that are of the type with which biotechnology companies usually wish to form strategic alliances; these are the few companies with global reach, extensive R&D operations and apparently copious amounts of cash. It is noteworthy how many biotechnology companies announce, publicly or privately, their plans (or perhaps hopes) to partner with Glaxo/Wellcome, SmithKline Beecham, Bayer, Bristol-Myers Squibb, Novartis and just a handful of other big players.

The second dimension of asymmetry is in terms of cash; the major pharmaceutical companies have it and the biotechnology ones do not. In fact, an amount of cash that would constitute a worth-while injection for a biotechnology company, especially with the implied technological validation accompanying it, verges on the level of petty cash for a pharmaceutical major. The average level of initial payment by the ten majors is less than US$9m and mid-sized European companies typically put up less than US$5m.[6] Amounts like this may be a life-line for a biotechnology company but US$10m represents less than 0.5 per cent of the total R&D budget of a leading company in the pharmaceutical industry.

The nature of partnership arrangements has to be viewed in the light of these two asymmetries. The big pharmaceutical companies are not going to be able to absorb all the projects brought to them; indeed, according to Lex in the *Financial Times*[7] 'executives at some big companies are complaining that they have too many plausible drug candidates to take forward'. Thus, the pharmaceutical companies are obliged to turn down many, if not most, of the partnership projects they are offered. But at what stage should they logically turn them down? It seems unlikely that this will be on first offering, provided that the biotechnology company makes out a reasonable case. Later on, when expenditure is likely to increase, the pharmaceutical company will have to thin its portfolio by dropping projects that are judged less likely to perform, clash with other candidates (whether from internal or

external sources), have too small a market potential, face tough competition or are expensive to manufacture. R&D directors have many reasons to discontinue projects and they are accustomed to being very choosy when limited resources have to be used wisely.

Discontinuing a project that is judged, inside the pharmaceutical company, to be relatively unpromising is no great hardship to it; in contrast, this action is a devastating, and sometimes fatal, blow to the biotechnology company that originated the product. Despite protestations to the contrary in the early stages of a partnership, the pharmaceutical company is only prepared to take a limited risk and will be ruthless in dropping projects that do not perform well enough against unadvertised criteria or in competition with other projects, in similar or different categories, which are also demanding access to the large-scale financial and other resources needed for late-stage development.

The fact that pharmaceutical companies do not develop all the products available to them is amply demonstrated by the fact that they not infrequently license compounds 'off-the-shelf' to smaller companies. SmithKline Beecham allowed Neurex to develop Corlopam despite its own decision to drop the product.[8] Vanguard Medica was established specifically to make the most of products that have been shelved or only partially developed by pharmaceutical companies; it reports good progress on a number of such compounds.[9]

If pharmaceutical companies cannot develop to market all the products brought to them by ambitious and hopeful biotechnology companies, why do they enter into alliances? The answer is clearly expressed in the customary phrase of 'keeping the options open'. It could also be expressed in terms of making sure that if the product is a really good one, it should not be allowed to go to a competitor. What the pharmaceutical company is doing is purchasing an option, very much in the same sense that its Treasury Department purchases options in the financial markets to hedge risk. Financial options give a right, but not an obligation, to exercise a later transaction. Options are risk management tools for buyers of them; they are risk-taking devices for those selling them. In the purchase and sale of a financial option, risk is transferred from the buyer to the seller.

In a biotechnology/pharmaceutical partnership the biotechnology company is the option seller and the pharmaceutical company is the option buyer. The option is really the right to sell a product in the future and to pay a royalty when doing so. By purchasing the option, the pharmaceutical company has that right but may not have the obligation (because it has lots of possible reasons for dropping a product). As far as the option seller is concerned the option commits it to a risk that the royalty flow will not be forthcoming, and to that decision being taken in a forum beyond its power to influence. Thus, the third asymmetry in the biotechnology/pharmaceutical partnership is risk. That this risk is real can be seen from a few examples of biotechnology companies suffering from projects being discontinued by their partners:

- Celltech granted a licence to Bayer for its BAY-X-1351 product for the treatment of septic shock. Celltech's annual report for 1996 showed this project to be its most important (it was listed number one in the highlights of the year) with the expectation that applications for marketing approval would be made in mid-1997. Yet in May, 1997, Bayer announced that it was no longer interested in the product following reports of trials' results. Celltech's market capitalisation fell by some 50 per cent in a few days. It is interesting to note that while Celltech's annual report commented fulsomely on the product, Bayer's 1996 annual report did not make a feature of it, although a number of other biotechnology alliances with named biotechnology companies were recorded in some detail.

- In its early years, the lead product of Cantab Pharmaceuticals was an antibody that was expected to reduce the problem of rejection in kidney transplantation significantly. The product was licensed to Baxter. That company's announcement of poor results in a Phase II trial came through in the course of Cantab's annual general meeting. Cantab's shares fell so far that its market capitalisation went below its cash reserves. Baxter was able to identify other products to develop.
- The Colorado drug delivery company, Verex, carried out extensive development work on a sustained release version of Glaxo/Wellcome's zidovudine which is marketed as Retrovir for use against AIDS. Verex claimed that its product, Aztec, was superior to Retrovir on all parameters examined in Phase III trials.[10] In contrast, a spokeswoman for Glaxo/Wellcome stated that it had thoroughly examined the data on Aztec, validating it by scientific and commercial criteria, but that it offered no significant benefit over Retrovir. Trade journal sources implied that Verex, with no other significant products, would have a very uncertain future as a result.

Of course a particular, and growing, risk to biotechnology/pharmaceutical partnerships became visible when a merger between Glaxo/Wellcome and SmithKline Beecham was proposed. There may be biotechnology companies which deliberately chose to work with one of these two pharmaceutical companies rather than the other, because of a competitive clash, a personality difference or because of a rejection. The merger announcement recreated problems for such companies. Indeed, the share price of Vanguard Medica became volatile after the merger announcement because its lead product, VML 251, which had been licensed to SmithKline Beecham, would have competed with Glaxo/Wellcome's own research products naratriptan and sumatriptan. Even if the new merged company had wanted to take on the product it is possible that the competition authorities would have vetoed this.

Alternative models

If partnering, as practised in recent years, represents a risk to biotechnology companies it is essential to ask what alternatives are available to them. There are several options that might be considered and these are briefly discussed below.

Multi-party alliance

This is a development of the typical partnering process in which a large number of companies come together in an alliance in which all contribute something that is deemed to be essential. Typically, there is a leader which is a large pharmaceutical company with an identified need. The RPR–Gencell scheme is one example, while Pfizer has organised a consortium and the SmithKline Beecham link with Human Genetic Sciences (HGS), and other companies, has some similarities. The advantage to the biotechnology companies involved is that the pharmaceutical company has to contribute such a large financial resource that it has to make the alliance work. While this is true in general it may not be true for every member; indeed a member failing to deliver (or judged to be so) may be ejected and replaced. The RPR–Gencell grouping has had some changes of membership. Additionally, the smaller companies may have no opportunity to retain any real lives of their own and may become mere appendages of the coordinating company.

Bootstrap

In this model the biotechnology company seeks to keep almost complete control of the development process. The key word is control because it admits that the company may not do all the work itself but may contract out those things that it cannot do or does not want to do. The difficulty with this approach is that it returns to the older model, demanding enormous financial resources be raised by the company, which even Genentech and Chiron were

ultimately unable to maintain, although Amgen did. Yet Genentech did maintain it for long enough to achieve very considerable value which could be released to the patient shareholders when Roche paid an attractive price for majority control. One company which was intending to pursue this strategy was British Biotechnology although recent events (May 1998) suggest a reconsideration. It has raised very large sums, more than US$200m in one single financing, and its marimastat nears the end of the clinical programme. Given an attractive story, combining technology and management, it appears that the markets may be willing to accommodate this model; perhaps it will be considered by other companies in the future. This strategy would allow the biotechnology company to retain control of the development process; it may nurture the product more than a partner would and the final decision to license marketing rights, if one is made at all, would be made only at the time of product approval, when the monetary value of the deal is likely to be at its maximum potential level.

An alternative way of achieving bootstrapping could be with the aid of a well-capitalised company which has no interest in selling products; in this version a contract research organisation, for example, commits its skills to helping a fledgling company, which operates as a virtual company, to develop its products but takes at least part of its reward in deferred payments and/or in equity.

Low-margin products

A company with some product sales can commit the profits from them to the successful development of other products. Thus, several biotechnology companies have first developed products that have lower regulatory requirements or faster development paths. The most obvious approach has been through diagnostics, although this has often been disappointing as diagnostic sales have been smaller than anticipated and development paths longer. Other approaches are over-the-counter (OTC) sales (Scotia used this route) or the acquisition of established products in market sectors relevant to core development targets. The latter route is particularly appropriate for companies that need to establish a sales force in advance of launching a new proprietary product. Neurex has adopted this approach through its acquisition of Corlopam from SmithKline Beecham. It plans to recruit a sales force of some 30 people to sell to about 600 centres in the USA; this is acknowledged by the company[8] to create the basis for eventually selling its key development product, SNX-111, which is targeted at the same outlets. A particular technological skill can also be a way to early revenues. For many years Celltech used its subsidiary Celltech Biologics to generate revenues through the contract manufacture of antibodies for third parties. Hybridon was similarly able to contract manufacture oligonucleotides for others; moreover, by doing so it was able to polish its skills in this area in advance of the commercialisation of its own products. Management theorists would recognise this strategy as using a *cash cow* to support a future *star*.[11]

All of these routes have been used to generate revenues and profits but there are indications that this is not a sustainable strategy.[12] Concern has been expressed, not least by influential investors and market analysts, that the existence of, and need to manage, a revenue source distracts management from its primary task of developing the core business. Celltech disposed of its Biologics subsidiary to Lonza precisely for this reason, and the sale generated a useful injection at a time when the parent company's need for cash was relatively high.

Platform technologies

A considerable number of biotechnology companies have disavowed any intention to sell products. They present themselves as having methods of helping other companies to develop through the use of so-called

platform technologies. In theory such specialists avoid product risk and can have a wide portfolio of projects and customers. Examples include companies in combinatorial chemistry and high throughput screening (eg Pharmacopeia), genomics (Hexagen), chirality (Celgene), bioinformatics (Oxford Molecular) and drug delivery (Alza). It appears that companies following this strategic approach expect to achieve profitability earlier, and consume less cash in doing so, than companies that focus on products. On the other hand, the barriers to entry that such companies can erect are not so high as they are with a unique and patented entity such as a drug. Consequently, once they have demonstrated a new capability they can expect imitators. This was particularly apparent in the case of combinatorial chemistry where the first entrant, Affymax, recognised that the best strategic option was to give up its independence through a sale to a leading company, Glaxo, which could use its skills in its own discovery programmes. Steven Holtzman of Millennium Pharmaceuticals has been reported to have said 'most single technologies do not a business make'. Some platform companies have changed their strategies after relatively short periods; Chiroscience no longer sees itself as the chirality specialist, which it was when going through its flotation (initial public offering), but now sees itself as a pharmaceutical company.

Consolidation

One of the characteristics of biotechnology companies is that they have small product portfolios while successful pharmaceutical companies tend to have large ones. If biotechnology companies are vulnerable as a result then they could, in principle, join together to achieve larger product portfolios, making them less vulnerable. Alternatively, they could seek to build complementary technologies to enhance the rate of product discovery; this has been the approach adopted by Chiroscience through its merger with Darwin. Consolidation is a risk-reduction strategy although it is not yet clear that the financial markets view it in that light, let alone biotechnology company managements.

The first significant biotechnology/biotechnology deal was between Arris and Khepri. In 1997 the Genzyme/Pharmagenics, Cell Genesys/Somatix and Agouron/Alanex deals all fall into this class. Before Arris/Khepri, most previous consolidations between biotechnology companies arose from significant weakness on the part of one of the companies. Synergen and Cetus were both consumed after they had had disastrous results in late-stage trials programmes.

Biotechnology companies hope to sell their products, and sometimes their dreams of products, to large pharmaceutical companies. There is a significant move to consolidate in the pharmaceuticals sector as has been demonstrated by Ciba and Sandoz forming Novartis and by the now terminated discussions between Glaxo/Wellcome and SmithKline Beecham. As a direct result of the latter it appears that several other large companies are now in play, not least American Home products which was turned down by SmithKline Beecham but which subsequently announced a deal with Monsanto. Can the biotechnology sector avoid consolidation when the companies with which it wants to partner are themselves consolidating?

Conclusions

Biotechnology companies are attracted to deals with pharmaceutical companies because of the direct cash receipts and the validation that provide access to public markets. But, the partner may not lavish upon the property the same care and attention as the originator would and is highly likely to drop most of the products that have been offered to it. The impact on a biotechnology company is devastating. Biotechnology companies need to consider alternative strategies whereby they accept

less risk than is implied by the current partnering model. Strategy innovation is required.

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